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Review Article

A REVIEW REPORT ON LYRICA (PREGABALIN) AS ANTIEPILEPTIC AGENT

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Abstract

Epilepsy is a chronic disorder of the central nerve system (CNS). It affects 5-10 per 1000 of the general population. There are different types of epilepsies. For the identification of different kinds of epilepsies different test and physical examination will perform by the doctors, further to treatment of this disease the treatment involves surgery and medication. For medication of this disease many kinds of antiepileptic drugs are available which are divided into many chemical classes. Lyrica pregabalin is the new antiepileptic drug which is introduced as an antiepileptic agent in 30th December 2004 by the FDA. It is a structural derivative of the inhibitory neurotransmitter gamma amino butyric acid (GABA). Dizziness and drowsiness are the most common (>10 % patients) adverse effect of pregabalin. A hypersensitivity to pregabalin or other component of the product may develop, resulting in an unfavorable interaction with the body. Pregabalin cross the blood-brain barrier in mice, rats, and monkeys. Approximately 98 % of the radioactivity recovered in the urine was unchanged pregabalin. N-methyl is the major metabolite of pregabalin. It has been assigned to pregnancy category 'C' by the FDA. Pregabalin is also used off-label for the treatment of chronic pain, neuropathic pain, preoperative pain, and migraine. The maximum dosing regimen is 600 mg/day.

Keywords: Gamma amino butyric acid (GABA), hypersensitivity, dosing regimen.

INTRODUCTION

The term "epilepsy" is derived from the Greek word "epilambanein", which means "to seize upon", "to attack". Johan Jackson; who is considered as the father of modern concepts of epilepsy; nearly 1 % of the world's populations suffer from epilepsy¹. The term epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. Seizures can be "nonepileptic" when evoked in a normal brain by treatments in such as electroshock or chemical Convulsions or

"epileptic" when occurring without evident provocation². The episodic manifestations of epilepsy are dependent on the portions of the CNS involved. There are very different types of seizure, it is better to speak of epilepsies. Epilepsy is usually only diagnosed after the person has two seizures or more. The brain is responsible for all the functions of our mind and body. Seizures can happen in any part of the brain³. Epilepsy is most commonly developed in older age and an accurate diagnosis in the elderly is crucial. Elderly people have 2-3 times higher mortality than the general population⁴.

Figure 1: Schematic representation of different causes of epilepsy

WHO estimates that eight people per 1000 worldwide have this disease. The prevalence of epilepsy in developing countries is usually higher than in developed countries. Over half of the 50 million people with epilepsy worldwide are estimated to live in Asia⁵. About 80 % of the burden of epilepsy is in the developing world, where in some areas 80–90 % of people with epilepsy receive no treatment at all. A total of about 43 704 000 people with epilepsy are reported

from 108 countries covering 85.4 % of the world population. Data regarding the inclusion of first-line antiepileptic drugs in the country's list of essential drugs show that Phenobarbital is included in 95 % of the responding countries, carbamazepine in 93 %, phenytoin in 86 % and valproic acid in 87 %. Migralepsy terminology use for “visual symptoms followed by migraine and subsequently by symptoms characteristic of epilepsy”^{6,7}.

Structure of the brain

Figure 2: Schematic representation of different parts of human brain

Pathophysiology

The convulsion result from sudden hyper synchronization of electrical discharge in neuronal networks in an apparently normal or a diseased cerebral cortex. The mechanisms and reasons for the discharge are not well understood. One hypothesis is that a group of diencephalic neurons normally exerts a constant inhibitory influence on cortical neurons, thereby preventing excessive discharge. In epilepsy, the neurons are different, supersensitive and susceptible to activation or depolarization by a variety of stimuli. Seizures may result from a reduction of inhibitory neurotransmission mediated by the neurotransmitter gamma-aminobutyric acid (GABA) or by enhancement of the excitatory neurotransmitter system mediated by glutamate and aspartate. During a seizure, consciousness may be unaffected, lost completely, or altered but not completely lost. Patients may experience only minor interruptions in their motor activity or they may experience intense muscular activation that leads to

motor behavior characteristic of generalized tonic-clonic seizures³.

General symptoms of epilepsy

The symptoms of epilepsy vary from person to person. Some people may have simple staring spells, while others have violent shaking and loss of alertness. The type of seizure depends on the part of the brain affected and cause of epilepsy^{8,9}.

- Seizures
- Convulsions
- Abnormal body movements
- Loss or disturbed consciousness

Type of seizure

Seizures have been classified into two broad groups: partial (focal), and generalized.

Figure 3: Classification of different types of seizure¹⁰

Partial

The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain.

Simple partial

These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity, which are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness.

Complex partial

These seizures exhibit complex sensory hallucinations, mental distortion, and loss of consciousness. Motor dysfunction may involve chewing movements, diarrhea, or urination. Eighty percent of individuals with complex partial epilepsy experience their initial seizures before twenty years of age.

Generalized

These seizures begin locally, but they rapidly spread, producing abnormal electrical discharges throughout both hemispheres of the brain. Generalized seizures may be convulsive or non convulsive, and the patient usually has an immediate loss of consciousness.

Tonic-clonic (grand mal)

This is most commonly encountered- and the most dramatic- form of epilepsy. Seizures result in loss of consciousness,

followed by tonic (continuous contraction) and then clonic (rapid contraction and relaxation) phases. The seizure is followed by a period of confusion and exhaustion due to the depletion of energy stores.

Absence (petit mal)

These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset occurs in patients at three to five years of age and lasts until puberty. The patient stares and exhibits rapid eye-blinking, which lasts for three to five seconds.

Myoclonic

These seizures consist of short episodes of muscle contractions that may reoccur for several minutes. Myoclonic seizures are rare, occur at any age, and are often a result of hypoxia, uremia, encephalitis, or drug poisoning.

Febrile seizures

Young children (3 months to 5 years of age) frequently develop seizures with illness accompanied by high fever. The febrile seizures consist of generalized tonic clonic convulsions of short duration. Although febrile seizures may be frightening to observers, they are benign and do not cause death, neurologic damage, injury, or learning disorders, febrile seizures require medication.

Status epilepticus

These seizures are rapidly recurrent.

Figure 4: Schematic representation of different MOA of antiepileptic drugs

Table 1: Different classes of seizures with their causes and symptoms

Types of seizure	Absence (petit mal) seizure	Generalized tonic-clonic (grand mal) seizure	Partial (focal) seizure
Causes	Occur most often in people under age 20, usually in children ages 6 to 12. They may occur with other types of seizures, such as generalized tonic-clonic seizures (grand mal seizures), twitches or jerks (myoclonus), or sudden loss of muscle strength (atonic seizures).	It may occur in people of any age. They may occur once (single episode) or as part of a repeated, chronic condition (epilepsy).	By abnormal electrical disturbances in the brain.
Symptoms	Occur many times a day Occur for weeks to months before being noticed Be mistaken for lack of attention or other misbehavior During the seizure, the person may: Stop walking and start again a few seconds later The person usually does not fall during the seizure.	Biting the cheek or tongue Clenched teeth or jaw Loss of urine or stool control (incontinence) Stopped breathing or difficulty breathing Blue skin color After the seizure, the person may have: Normal breathing Sleepiness that lasts for 1 hour or longer Loss of memory (amnesia) regarding events surrounding the seizure episode Headache Confusion Weakness of one side of the body for a few minutes to a few hours following seizure (called Todd's paralysis).	Abnormal muscle contraction Lip smacking Chewing/swallowing without cause Forced turning of the eyes Nausea Sweating Flushed face Dilated pupils Rapid heart rate/pulse Blackout spells periods of time lost from memory

Examination and Tests

The doctor will perform a physical examination, which will include a detailed look at the brain and nervous system. An EEG (electroencephalogram) will be done to check the electrical activity in the brain. The brain may appear normal after a seizure or between seizures¹¹. Up to 5 % people without epilepsy may have nonspecific abnormalities in their EEG recording; while up to 40 % of people with epilepsy may have a normal EEG recording between seizures⁴.

Tests that may be done include:

Blood chemistry
Blood sugar
CBC (complete blood count)
Kidney function tests
Liver function tests
Lumbar puncture (spinal tap)
Tests for infectious diseases

Figure 5: Electroencephalography (EEG) recording of different seizure in human brain

Treatment Medication

To prevent seizures, called anticonvulsants, may reduce the number of future seizures. These drugs are taken by oral route. These are prescribed depends on the type of seizures. Many epilepsy medications cause birth defects. Women wishing to become pregnant should tell the doctor in advance in order to adjust medications. Epilepsy that does not get better after two or three anti-seizure drugs have been tried is called

"medically refractory epilepsy". Bromide (1857) was the first drug to be used for the treatment of epilepsy, but it is now obsolete.

Surgery

If epilepsy seizures are due to a tumor, abnormal blood vessels, or bleeding in the brain, surgery to treat these disorders may make the seizures stop. Epilepsy surgery is available in 40.9 % of the responding countries^{11,12}.

Table 2: Different classes of antiepileptic drugs with their chemical structure

CLASSIFICATION OF ANTIEPILEPTIC DRUGS ¹³⁻¹⁵		
Barbiturate	Phenobarbitone (Luminal)
Deoxybarbiturate	Primidone
Hydantoin	Phenytoin (Dilantin)	Fosphenytoin
Iminostilbene	Carbamazepine	Oxcarbazepine
Succinimide	Ethosuximide (Zarontin)
Aliphatic carboxylic acid -	Valproic acid (sodium valproate)	Divalproex

Benzodiazepines	Clonazepam Diazepam Lorazepam Clobazam
Phenyltriazine	Lamotrigine
Cyclic GABA analogue	Gabapentin
Newer drugs	<div style="display: flex; flex-wrap: wrap;"> <div style="width: 50%;"> Vigabatrin </div> <div style="width: 50%;"> Topiramate </div> <div style="width: 50%;"> Tiagabine </div> <div style="width: 50%;"> Zonisamide </div> <div style="width: 50%;"> Levetiracetam </div> </div>

MODERN TREATMENT OF EPILEPSY

LYRICA (PREGABALIN)

LYRICA APPROVAL HISTORY¹⁶

FDA approved: First approved December 30th, 2004

Brand name: Lyrica

Generic name: Pregabalin

Company: Pfizer Inc.

Treatment for:

Neuropathic pain

Post herpetic neuralgia

Fibromyalgia

Diabetic peripheral neuropathy

Epilepsy

Lyrica (pregabalin) is a structural derivative of the inhibitory neurotransmitter gamma amino butyric acid indicated for the

management of neuropathic pain associated with diabetic peripheral neuropathy, post herpetic neuralgia and spinal cord injury; as an adjunctive therapy for partial onset seizures and for the treatment of fibromyalgia.

Clinical Results of Lyrica (Pregabalin)

Lyrica (pregabalin) is a modulator of voltage-gated calcium channels, designed to affect neurological transmission in multiple systems. Lyrica is specifically indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, and post herpetic neuralgia. It is also indicated as an adjunctive therapy for the treatment of adult patients with partial onset seizures. Lyrica is supplied as a hard-gelatin capsule for oral administration¹⁷.

Table 3: Pregabalin initial dosing for treatment of seizures

Disease	Initial dosing for treatment
Neuropathic pain	50 mg thrice daily, with escalation permissible to 100 mg thrice daily within 1 week in patients with creatinine clearance of at least 60 ml/min, based on tolerability and efficacy.
Post herpetic neuralgia	75 mg twice daily or 50 mg thrice daily (in patients with creatinine clearance >60 ml/min), with escalation to 150 mg twice daily or 100 mg thrice daily (in patients with creatinine clearance >60 ml/min) permissible.
Adjunctive treatment of epilepsy	150 mg twice daily or 100 mg thrice daily (in patients with creatinine clearance >60 ml/min) permissible. For the adjunctive treatment of epilepsy, recommended initial dosing is 150 mg daily (as 50 mg thrice daily or 75 mg twice daily), with escalation to a maximum total daily dose of 600 mg (200 mg thrice daily or 300 mg twice daily) based on efficacy and tolerability.

Note: Lyrica therapy, dosing should be tapered over at least 1 week.

Table 4: Chemical nature and properties of Pregabalin

Molecular Formula	C ₈ H ₁₇ NO ₂
Molecular weight	159.23
pKa1	4.2
pKa2	10.6
pH	7.4 – 1.35
Chemical structure
Solubility	Freely soluble in water and both acidic and basic solution
Half life	6.3 hours
Dose size	25 – 300 mg
Dosage forms	Solid, liquid (20 mg/ml)

Pharmacology

Pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-amino butyric acid (GABA); however, it does not directly bind to GABA receptors. Pregabalin binds to the alpha2-delta site of voltage-gated calcium channels in the central nervous system (CNS) tissues. This calcium channel modulation may reduce the release of many neurotransmitters. Like gabapentin, the precise mechanism of action of Pregabalin is unknown. Gabapentin differs from Pregabalin because of the reduced binding affinity to voltage-gated calcium channels. Pregabalin is six-times more potent than gabapentin in

binding affinity to the alpha2-delta voltage-gated calcium channel. The manufacturer states that 50 mg of Pregabalin is approximately equal to 300 mg of gabapentin. This alteration of calcium channel function is not to be confused with calcium-channel blockers. Pregabalin and gabapentin alter channel function without complete blockade of the calcium channel resulting in virtually no change in systemic blood pressure or coronary blood flow changes¹⁸.

Mechanism of action (MOA) of Lyrica (In diagram)

Lyrica is thought to rebalance neurotransmitters involved in central pain amplification¹⁹

Figure 6: Schematic representation of MOA of Lyrica

Table 5: Adverse drug reactions associated with the use of Pregabalin

Condition	Adverse effects
Very common (>10% of patient)	Dizziness, drowsiness.
Common (1-10% of patients)	Blurred vision, diplopia, increased appetite, euphoria, confusion, vivid dreams, changes in libido (increase or decrease), irritability, ataxia, attention changes, abnormal coordination, memory impairment, tremors, dysarthria, paresthesia, vertigo, dry mouth and constipation, vomiting and flatulence, erectile dysfunction, fatigue, peripheral edema, drunkenness, abnormal walking, weight gain, asthenia, nasopharyngitis, increased creatine kinase level.
Infrequent (0.1-1% of patients)	Depression, lethargy, agitation, anorgasmia, hallucinations, myoclonus, hypoaesthesia, hyperaesthesia, tachycardia, excessive salivation, sweating, flushing, rash, muscle cramp, myalgia, arthralgia, urinary incontinence, dysuria, thrombocytopenia, kidney calculus.
Rare (<0.1% of patients)	Neutropenia, first degree heart block, hypotension, hypertension, pancreatitis, dysphagia, oliguria, rhabdomyolysis, suicidal thoughts or behavior.

Note: Pregabalin may also cause withdrawal effects after long-term use if discontinued abruptly.

Adverse effects

Over dosage

Several renal failure patients developed myoclonus while receiving pregabalin, apparently as a result of gradual accumulation of the drug. Acute over dosage may be manifested by somnolence, tachycardia and hypertonicity. Plasma, serum or blood concentrations of pregabalin may be measured to monitor therapy or to confirm a diagnosis of poisoning in hospitalized patients.

Pharmacokinetics

Absorption

Pregabalin oral bioavailability is estimated to be greater than or equal to 90 % and is independent of dose. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25 to 30 % and a delay in t_{max} of approximately 2.5 hours. Administration with food, however, has no clinically significant effect on the extent of absorption²⁰.

Distribution

Pregabalin cross the blood–brain barrier in mice, rats, and monkeys. It has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the volume of distribution of pregabalin for an orally administered dose is approximately 0.56 L/kg and is not bound to plasma proteins.

Metabolism

Approximately 98 % of the radioactivity recovered in the urine was unchanged pregabalin. The major metabolite is N-methyl pregabalin.

Excretion

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Renal clearance of pregabalin is 73 ml/minute.

Drug Interactions

The manufacturer notes some potential pharmacological interactions with opioids (pregabalin is synergistic with opioids in lower doses), benzodiazepines, barbiturates, ethanol (drinking alcohol), and other drugs that depress the central nervous system. A hypersensitivity to pregabalin or other component of the product may develop, resulting in an unfavorable interaction with the body²⁰.

Pregnancy

Pregabalin has been assigned to pregnancy category ‘C’ by the FDA. Animal studies have revealed increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity including lethality, growth retardation and both nervous and reproductive system functional impairment. Animal studies have reported that pregabalin crosses the placenta and have shown an increased risk in male-mediated teratogenicity. There are no controlled data in human pregnancy. Pregabalin should only be given during pregnancy when there are no alternatives and benefit outweighs risk.

Major seizures- major seizures are harmful to the developing fetus because of the possibility of anoxia and metabolic disorder.

Minor seizures- Minor seizures are probably harmless and therefore need not be eradicated.

Breast feeding

While taking pregabalin may cause risk to the infant because the drug has been shown to be excreted in the breast milk of rats. Human studies are unknown, but the use of pregabalin while breast feeding is not recommended. Anti-epilepsy drugs pass into breast milk, Phenobarbital, primidone and ethosuximide in significant quantities, phenytoin and sodium valproate less so¹².

High risk group

The drug should not be given to pregnant mothers, cardiac / hypertensive patients, patients suffering from kidney dysfunction and geriatrics.

Warnings and precautions

Do not drink alcohol while taking pregabalin. Alcohol can add to the drowsiness caused by this medication. The Doctor should be informed if the patient is allergic to pregabalin. Caution should be exercised when prescribing pregabalin to patients who have had a previous episode of angioedema.

Figure 7: LYRICA 75 mg capsules the brand of Pfizer

Uses

Pregabalin is also used off-label for the treatment of chronic pain, neuropathic pain, preoperative pain, and migraine. Usually physicians will start the patient on a low dose of pregabalin and increase it gradually, depending on the patient's evaluation. Its therapeutic effect appears after 1 week of use and is similar in effectiveness to lorazepam, alprazolam and venlafaxine but pregabalin has demonstrated superiority by producing more consistent therapeutic effects of psychic and somatic anxiety symptoms. Long-term trials have shown the continued effectiveness without the development of tolerance and additionally unlike benzodiazepines it does not disrupt sleep architecture and produces less severe cognitive and psychomotor impairment; it also has a low potential for abuse and dependence and may be preferred over the benzodiazepines for these reasons. There is not enough data to state that it should be used in all neuropathic pain, and it has not been found to be effective for HIV-associated peripheral neuropathy^{18,19}.

Storage conditions of Pregabalin

Capsules: Store in a well closed container, between 15°C-30°C. Protect from moisture and heat¹⁹.

CONCLUSION

Lyrica (Pregabalin) is specifically indicated for the treatment of neuropathic pain associated with spinal cord injury. It is also indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, for post herpetic neuralgia, for fibromyalgia, and as an adjunctive therapy for adults with partial onset seizures. Lyrica is supplied as a hard-gelatin capsule for oral administration. The recommended initial dose of the drug for the treatment of neuropathic pain associated with spinal cord injury is 150 mg/day (75 mg twice/day), which can be escalated to 300 mg/day within the first week. The maximum dosing regimen is 600 mg/day.

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